SCIENCE

VOL. 101 FRIDAY, JANUARY 19, 1945 No. 2612

Blood Proteins and Their Therapeutic Value: PROFESSOR EDWIN J. COHN 51

Obituary:
Deaths and Memorials 57

Scientific Events:
Vital Statistics of Australia; Meetings of Entomologists; The Annual Meeting of the American Phytopathological Society; The National Malaria Society; The Bernays Radio Award 57

Scientific Notes and News 59

Discussion:
The Nomenclature of the Rh Blood Types: DR. LAURENCE H. SNYDER. *The Threat to Pure Science:* DR. JARED S. MOORE. *Gaps in Current Files of Scientific Periodicals:* EILEEN R. CUNNINGHAM. *Education in Argentina:* PROFESSOR J. A. SHELLENBERGER 62

Scientific Books:
Advanced Calculus: PROFESSOR D. V. WIDDER. *The Needs of Man:* DR. WARREN S. THOMPSON 64

Special Articles:
Interaction between Crystalline Penicillin and Human Plasma Proteins: DR. BACON F. CHOW and CLARA M. MCKEE. *The Serological Diagnosis of Syphilis:* DR. HANS NEURATH and OTHERS. *A New Trypanocidal Agent: γ-(p-Arsenosophenyl)-Butyric Acid:* DR. HARRY EAGLE 67

Scientific Apparatus and Laboratory Methods:
A Microcalomel Electrode for Polarographic Measurements: DR. PHILIP W. WEST and DR. EDWARD S. AMIS 71

Science News 10

SCIENCE: A Weekly Journal, since 1900 the official organ of the American Association for the Advancement of Science. Published by the American Association for the Advancement of Science every Friday at Lancaster, Pennsylvania.

Editors: JOSEPHINE OWEN CATTELL and JAQUES CATTELL.

Policy Committee: MALCOLM H. SOULE, ROGER ADAMS and WALTER R. MILES.

Advertising Manager: THEO. J. CHRISTENSEN.

Communications relative to articles offered for publication should be addressed to Editors of Science, The Science Press, Lancaster, Pa.

Communications relative to advertising should be addressed to THEO. CHRISTENSEN, Advertising Manager, Smithsonian Institution Building, Washington 25, D. C.

Communications relative to membership in the Association and to all matters of business of the Association should be addressed to the Permanent Secretary, A.A.A.S., Smithsonian Institution Building, Washington 25, D. C.

Annual subscription, $6.00 Single copies, 15 cents

BLOOD PROTEINS AND THEIR THERAPEUTIC VALUE[1,2]

By Professor EDWIN J. COHN

DEPARTMENT OF PHYSICAL CHEMISTRY, HARVARD MEDICAL SCHOOL

RECOGNITION of the role of the National Research Council in making available to Government Agencies the knowledge and advice of civilian experts in the medical sciences appears to be peculiarly appropriate at this time. I am honored to have been asked to participate in this ceremony, and to discuss blood proteins and their therapeutic value. The Blood Substitutes Sub-Committee of the National Research Council is a small group, the membership of which has changed but little from the time, many months before Pearl Harbor, when it was reorganized and charged with the responsibility of advising the Armed Forces and Government Agencies as to the methods to be employed and the products to be accumulated against military emergency or civilian disaster. Although it has carefully and critically examined the properties of every blood substitute that has been suggested, it

[1] Address delivered on December 11, 1944, at the ceremony of the award to the National Research Council by the American Pharmaceutical Manufacturers Association, New York, N. Y.

[2] The observations on which this appraisal is based involve so many fields and have appeared in such diverse publications that even a partial bibliography would be longer than this address. "A Plan for Collection, Transportation and Administration of Whole Blood and of Plasma in Warfare," by DeGowin and Hardin (*War Medicine*, 1: 326, 1941), reviews the earlier experience on blood transfusions, "The Preparation and Preservation of Human Plasma," by Strumia, McGraw, and Reichel (*Am. Jour. Clin. Path.*, 11: 480, 1941), that on the drying of plasma from the frozen state, and "The Properties and Functions of the Plasma Proteins," (*Chem. Reviews*, 28: 395, 1941), the methods available for their separation and purification. Other references are given in a more recent report on "Blood, Blood Derivatives, and Blood Substitutes" (*Proc. Am. Philos. Soc.*, 88: 159, 1944), in a series of twenty-three communications from different laboratories under the title, "Chemical, Clinical and Immunological Studies on the Products of Human Plasma Fractionation" (*Jour. Clin. Investigation*, 23: 1944), and in four clinical papers that have appeared lately (*Jour. A. M. A.*, 126: 469, 674, 680 and 944, 1944).

has thus far recommended to the Armed Forces only products derived from human blood. Its membership has included the expert who recommended the methods for blood procurement on the basis of which the American Red Cross blood donor program has functioned so successfully; the expert on blood banks, who continuously stressed the place of whole blood in therapy; the expert on dried plasma whose knowledge and experience of many years in its preparation and administration have thus always been available; a professor of medicine; a professor of surgery, and myself, a chemist concerned with the properties of proteins, their separation and purification, and their biological functions.

These experts have met repeatedly with the designated representatives of the Surgeons General of the Army, the Navy, and the Public Health Service, the Red Cross, the Office of Civilian Defense, and the Food and Drug Administration, inviting other experts to meet with them as occasion demanded. Unburdened by an administrative hierarchy or intermediaries they have transmitted their advice directly and supplemented and implemented their recommendations with reports and memoranda on the value and safety of products and of chemical or biological processes. This is the form of civilian advisory function which President Lincoln envisaged in creating the National Academy of Sciences, and it is to be hoped that it will be the form of the agencies which will advise Government regarding the medical sciences in the post-war world.

Whole Blood. As a part of the symposium on some fundamental trends in chemotherapy you have asked me to discuss "Progress in Conquest of Knowledge of Blood Proteins and of Their Therapeutic Value." A question which at once arises is how much of the organization for the collection and processing of the human blood, that has been developed during this war, will continue in the post-war world. Whole blood and plasma were well-known therapeutic remedies before this war. Their value has been further proven in military theaters of operation. Whole blood is especially needed when there has been severe blood loss, or when major operations are to be performed in which severe blood loss is anticipated. The red cells which are responsible for the respiratory function of the blood, carrying oxygen to the tissues, are also needed to combat the anemia which frequently occurs in convalescence from wounds. The therapeutic value of the red cells is thus related to their physiological functions. The therapeutic value of other constituents of blood may also be related to their physiological functions.

The lability of whole blood made it necessary to prepare for this war by the accumulation of reserves of the more stable components of blood. However, work continues in many laboratories[3] in an attempt to increase the span of life of the labile cellular constituents of blood so as to render them available over longer periods of time. Progress in the preservation of red cells both in whole blood and in media in which they can be resuspended may be expected to continue at an accelerated rate because of the methods that are being developed and the knowledge that is being gained.

Many of the conditions for which whole-blood transfusions are used, notably where there is a need for the red blood corpuscles, can probably be successfully provided for by resuspended red cells. Others may be satisfied by the injection of plasma or of a plasma fraction. The longer life of the red cell in whole blood than resuspended in any medium at present known makes it necessary whenever possible to fly whole blood to our Armed Forces. The social economy of using cells and plasma separately in the therapy of different conditions, if either can be demonstrated to be as satisfactory as the whole for the conditions indicated, is, however, so advantageous as to demand consideration in the post-war world.

Plasma. The separated plasma can be stored in the liquid state, can be frozen or can be dried from the frozen state. In the liquid state it retains its colloidal properties necessary for the treatment of shock, but the more labile components of plasma, the prothrombin and fibrinogen, concerned with blood coagulation, complement and the antibodies, concerned with immunity, deteriorate with time. For an economical civilian program, therefore, liquid plasma has distinct limitations. In the frozen state, the labile components of plasma are better preserved; here the limitation is the inconvenience for storage and transport and immediate emergency use. In the dried state, most of the labile components of plasma are preserved. Dried plasma has been used by our Armed Forces since, processed to a stable state from the blood collected by the American Red Cross it, as other dried products, can be accumulated as a reserve against need at a future time and place.

Plasma was accumulated in this war largely for the prevention and treatment of shock. Shock as observed in military medicine generally results from a rapid decrease in the volume of circulating blood due to the loss of blood and plasma proteins externally and into damaged tissues. It is most frequently treated, or prevented by injection of plasma proteins. The injected proteins, in so far as they can not readily pass through the kidney, increase the body's reservoir of plasma proteins, and, in so far as they do not readily traverse the capillary walls, increase the

[3] Some under contract with the Committee on Medical Research of the Office of Scientific Research and Development.

plasma volume by drawing water from the tissues into the blood stream. The function of controlling the equilibrium between the water and the electrolytes in the blood and in the tissues is largely performed by the smaller proteins of the blood stream, known as albumins, although all dissolved colloids will, of course, exert some osmotic effect.

Albumin. The albumins of plasma represent less than 60 per cent. of the plasma proteins but are responsible for nearly 80 per cent. of the osmotic efficiency of the plasma, upon which its value in the treatment of shock largely depends. Human serum albumin has also been recommended by the Blood Substitutes Sub-Committee to the Armed Forces and, like plasma, it has been processed in large amounts from the blood collected by the American Red Cross. Unlike plasma, albumin is so stable that it can be dispensed in solution; the albumin molecules are so symmetrical that a 25 per cent. solution is iso-viscous with whole blood. The isoelectric, salt-free albumin is prepared as a dry, white powder; it can be redissolved at any concentration and with any diluent. As a concentrate poor in salt, it is proving of value as a diuretic agent. In the treatment of shock it functions as does plasma, largely by virtue of the albumin it contains, by pulling water back into the blood stream, and holding it there. This results in a decrease in viscosity and a restoration of the volume of circulating blood to normal, so that oxygen is transported to the tissues and the other physiological functions of blood are resumed.

Athough traumatic shock occurs frequently enough in civilian life, as a result of automobile, industrial or other accidents, to warrant a peace-time society making provision for its prompt treatment with adequate supplies of plasma or plasma derivatives, the control of certain infectious diseases with plasma derivatives appears to offer at least as great an opportunity for civilian medicine.

γ-Globulins. A large scale public health experiment has now supplemented earlier clinical studies in demonstrating the value of the γ-globulins of human plasma in the modification or prevention of measles. These γ-globulins have been separated from the same plasma which yielded the albumin employed in the prevention and therapy of shock.[4] Of the plasma proteins about 58 per cent. is albumin and 11 per cent. γ-globulin. Two fractions of γ-globulin may also be separated, the one richer in euglobulin and the other (Fraction II) in pseudoglobulin. The latter fraction, which has thus far been employed in the study of the control of infectious diseases, represents approximately 5 per cent. of the plasma proteins. None the less γ-globulin may come to be recognized as the most important fraction of the plasma from the point of view of public health.

Pooled normal or convalescent plasma has long been used in the control of certain infectious diseases. Many of the antibodies to the variety of infectious diseases to which the population contributing the blood has been exposed are γ-globulins. Moreover, it has been possible to demonstrate that a population shows heightened immunity following an epidemic of a special disease. The concentration of γ-globulin antibodies over the pooled plasma thus far achieved by fractionation is approximately 25-fold if we compare plasma with the concentrated solution of γ-globulins being made available to the Armed Forces and, through the Red Cross, to public health agencies.[5] As a result titers of certain antibodies, though not necessarily of all, are comparable to those of the corresponding convalescent sera. Therefore, in the prevention or treatment of any disease where the value of convalescent serum has been demonstrated, the effectiveness of a concentrate from pooled normal plasma should be investigated. If convalescent serum or hyper-immune serum is fractionated, still higher antibody titers may be obtained in the concentrated γ-globulins.

The antibodies effective in the modification or in the prevention of measles are present in the more soluble fraction (Fraction II) of the γ-globulins. This is true also of the antibodies for several other virus diseases. Effective use of the γ-globulins in the control of diseases other than measles has been reported. Should these preliminary studies be substantiated by large scale military or public health investigations, the need for γ-globulin may prove even greater than has thus far been anticipated. None the less it should be stressed that in the case of many diseases those bearers of immunity which are the antibodies of the blood stream can not be made available in amounts large enough, or injected soon enough to prevent the onset of disease. In others, the incidence of the disease in susceptibles is so small that it would be

[4] The program of plasma fractionation which has been developed in this laboratory was originally supported by grants from the Rockefeller Foundation and from funds of Harvard University. It was aided early in 1941 by grants from the Committee on Medicine of the National Research Council, which included a grant from the American College of Physicians. Since August, 1941, it has been carried out under contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Harvard University.

The insight of my many fellow workers in this department has been immeasurably aided by many colleagues—chemical, clinical, immunological and pathological—members of this or other universities, of the Armed Forces, of Committees of the National Research Council, of the American Red Cross or of the commercial laboratories with Navy contracts for plasma fractionation, who labored with us. Indeed, it would be impossible to list here the very large number of individuals and agencies who have collaborated in this work.

[5] See *J. A. M. A.*, 125: 635, 638, 1944.

necessary to immunize passively an entire population in order to offer protection to the one in a thousand who might contract the disease. The blood donors for such an undertaking might not always be available whereas blood donors conscious of the contribution that they were making to the control of other diseases could clearly always be counted on in a society which has responded as has ours in the blood donor program.

Two problems which are chemical, rather than clinical, have thus far limited studies to determine the most effective use of the γ-globulins. The progress that is being made, however, suggests that both are yielding to systematic scientific investigation. The first is concerned with the removal of depressor substances which have heretofore prevented the intravenous use of γ-globulin concentrates. Conditions for the separation of these substances and thus of the preparation of γ-globulins safe for intravenous use appear to have been found, however, and appraisal of the value of γ-globulin intravenously injected in diseases where larger amounts may be needed than can conveniently be administered intramuscularly has been begun. Intravenous injections of 25 cc have been given to small children with acute infections without reaction and 50 cc to children not acutely ill. The injection of a concentrate of γ-globulin equivalent to the amount which could be introduced as plasma or whole blood only by replacing the entire blood volume by transfusion would thus appear to be both possible and practicable. Chemical specifications for the routine production of such preparations are, however, not yet completely satisfactory.

The second chemical problem concerns the separation of the γ-euglobulins of the plasma (in Fraction III-1) from the isoagglutinins (blood typing globulins), cholesterol and carotenoid bearing β-globulins, so that clinical investigations with this potential source of antibodies may also be begun. The O typhoid agglutinin has been found concentrated in this fraction rather than in Fraction II. The possibility exists, however, that sub-fractionations of the γ-globulins may yield, in time, products derived from the same plasma, some of which are more potent concentrates of certain antibodies; some of others.

The Fractionation Process that we have developed yields all the components of human plasma in five major fractions. The number has purposely been made as small as possible so as to facilitate and render economical large scale processes. We shall not stop here to discuss the five-variable physico-chemical system upon which the separations depend except to state that it involves the principles determining electrostatic interactions between proteins and neutral salts, which generally lead to increased solubility, and interactions with less polar organic liquids, which generally lead to precipitating action. The balance between these forces has made possible the definition of conditions leading to far sharper separations than have previously been possible. The theory and general methods, though not the detailed procedures, are equally applicable to plasma and tissue extracts of plant or animal origin; that is, to all systems in which a large number of protein and lipid components are to be separated from each other and without loss of the biological activity upon which their therapeutic value depends.

When the method is applied to plasma, the fibrinogen, which is the structural element of the blood clot, is concentrated in Fraction I. Fraction II + III contains essentially all the prothrombin, which, converted to thrombin, transforms fibrinogen into fibrin; all the immune globulins for which tests have been carried out; the isohemagglutinins and Rh antibodies, of value in blood grouping, as well as all the carotenoids and such part of the cholesterol and phosphatides of plasma as appear to be associated with β- rather than α-globulins; the midpiece of complement; and probably innumerable other components of plasma which are not yet recognized by virtue of their chemical or biological properties. The remaining globulins are concentrated in Fraction IV.

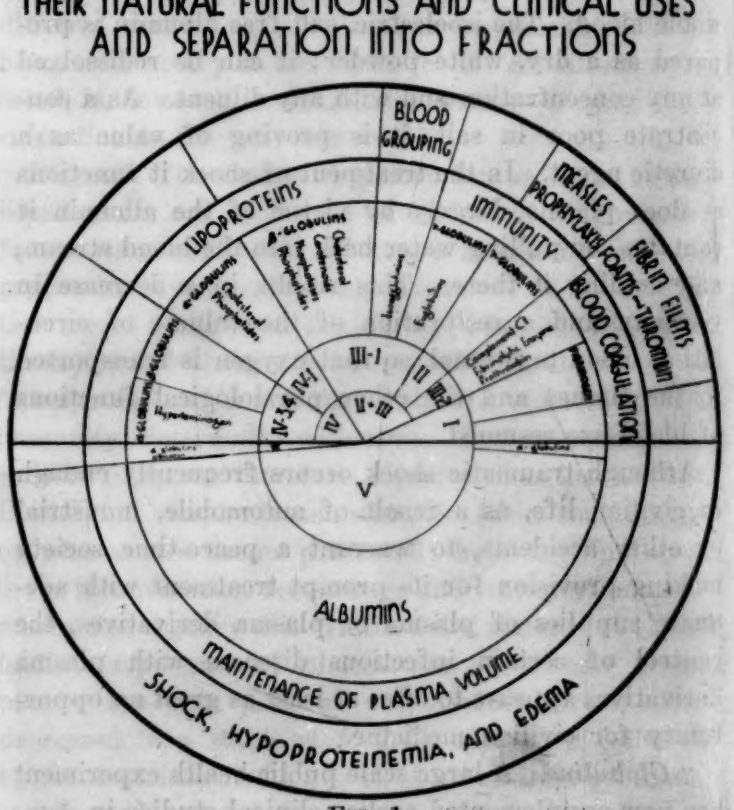

FIG. 1

Isohemagglutinins have also been prepared under contract with the Navy because of the value of these products of the fractionation of group specific plasma in the typing of whole blood. The products that have thus far been prepared commercially have been frac-

tionated respectively from pools of A or of B plasma. The presence of roughly four times as many A as B donors in our population has heretofore introduced an uneconomical factor in the preparation of blood grouping globulins from human plasma. Recently one of my collaborators has suggested and demonstrated the value of another method of segregating the plasma in pools for the preparation of isohemagglutinins. In this method the small number of B bloods are used to absorb the A anti-B agglutinins from O blood. The resulting fractionated and purified isoagglutinins are not only group specific but are far more avid with respect to the B anti-A_2 and A_2B sub-groups than the B anti-A agglutinins prepared from B plasma. And, of course, approximately five times as much of the product is obtained from an equal number of grouped bloods. This process thus makes available an almost equivalent amount of B anti-A and of A anti-B grouping material and greatly increases the economy of the preparation of these highly potent blood-grouping globulins.

The α- and β-globulins concentrated in Fraction IV have recently been subdivided into two fractions, both sufficiently stable to be dried from the frozen state and reconstituted as clear soluble protein concentrates. One of these sub-fractions (IV-1) contains the remaining lipids of the plasma which, in this preparation, appear to be associated with α-globulins, largely with α_1-globulins. The remainder of Fraction IV, tentatively designated IV-3, 4, is almost free of lipids, though rich in α- and β-globulins and is subject to further sub-fractionation in the interest of concentrating and purifying the diverse components which it contains.

In this process, all the proteins in plasma concerned with the coagulation process are concentrated in Fractions I and III-2; the immune globulins in II and III–1; the lipo-proteins in III–1 and IV–1 and the albumin in Fraction V which represents approximately 50 per cent. of the plasma proteins. Since the albumin in this fraction makes by far the largest contribution to the colloid osmotic pressure of plasma, fractionation yields albumin to perform this function and other fractions to be employed in therapy in connection with more specific physiological functions.

Not only has Fraction II been prepared in a state safe for intravenous use in the last months, but so also has Fraction IV-3, 4. What are the physiological functions and what are the therapeutic uses of this large fraction rich in α- and β-globulins, poor in lipids and antibodies and in components of the coagulation mechanism? The chemist is fulfilling his function when he makes these α- and β-globulins available in soluble, stable and safe form for intravenous use. We can depend on our clinical colleagues, armed with these tools, to determine the functions of these substances in the economy of the body and to discover their uses in therapy.

Fibrinogen, Thrombin and the Uses of Fibrin Products. In the subfractionation of Fraction II + III to yield the γ-globulin antibodies in Fraction II, prothrombin is of necessity first separated in Fraction III–2. Prothrombin may be converted to thrombin with human thromboplastin and large amounts accumulated and made available as a sterile dry powder ready for reconstitution and immediate emergency use. For stopping the flow of blood, in surgical procedures, thrombin is the only component of the clotting mechanism which must be supplied. For the most effective use of thrombin in hemostasis, however, it must be applied with a matrix which can hold the thrombin in the bleeding area until clotting is completed. A porous matrix soaked in thrombin solution can achieve this mechanical result. Fibrin foam is such a matrix formed from human fibrinogen and thrombin. It effectively controls bleeding from oozing surfaces and from veins, even very large ones. Though not recommended for brisk arterial hemorrhage, it has proved very effective in neurosurgery in controlling hemorrhage from the dura, from tumor beds, from dural sinuses and from large cerebral veins. In general surgery it has been reported effective, in a small number of patients, in controlling hemorrhage from the cut surface of the liver and kidney, in jaundice patients, in thorocic operations, and in stopping bleeding in hemophilia.

In the dry state fibrin foam is a porous material composed of strands of fibers separated by air spaces of macroscopic size. It readily absorbs water, saline or thrombin solution, and can be used in conjunction with a sulfa drug or with penicillin. The physical properties of the foam can be varied by controlling the conditions of manufacture. Since fibrin foam is prepared completely from human proteins and is rapidly absorbed with minimal tissue reaction, it may be left in place, thus preventing recurrence of bleeding. It is easily handled in the operating room, and, like serum albumin, is immediately available for use in emergencies.

Just as the asymmetry of certain synthetic polymers is responsible for the remarkable mechanical properties of industrial plastics, the fibrinogen molecule endows products of this human protein with remarkable mechanical properties. Among these products is fibrin film. Fibrin film may be prepared from fibrinogen and thrombin as a strong, rubbery sheet which can be stretched reversibly from two to three times its original length. This material can be made in various shapes and thicknesses, and in the form of seamless tubing. Its mechanical properties can also be varied

from a soft, rubberlike elasticity to a parchmentlike consistency.

The mechanical properties of the soft, rubbery films (as shown by their stress-strain curves) bear a marked similarity to those of the elastic ligament of the neck, the *ligamentum nuchae*. The tough films with delayed elasticity resemble rather wool or hair in their mechanical properties. It may be possible to imitate, with different types of fibrin products, still other natural structures of the body.

The fine structure of fibrin film has been shown to involve pores which in one type are of the order of 60 Ångstrom units in diameter. Hemoglobin molecules in solution pass through these pores readily, but plasma globulins are partially and fibrinogen molecules completely retained.

The mechanical properties of certain types of fibrin films make them suitable for use as dural substitutes and in the prevention of meningocerebral adhesions. The duration of their persistence in the body can be adjusted by suitable treatments. They have been used in neurosurgical operations and appear to be excellent materials for these purposes, patients having been followed for as long as fifteen months without the appearance of unfavorable sequelae. Other types of fibrin film and of fibrinogen plastics are being tested for other surgical applications.

Albumin and the immune globulins, fibrin foam and thrombin, have been licensed under the National Institute of Health, and have been prepared in large amounts under contract with the Navy. Fibrin films, which were developed in our laboratory several years ago, presented a considerable problem as a satisfactory sterilization procedure adaptable to their large scale preparation remained to be developed. I am happy to be able to report that a satisfactory procedure in which the films are sterilized by steam in the final container has been developed and is making large numbers of films prepared in this way available for final appraisal.

In Summary, the knowledge of blood proteins and their therapeutic value that has been gained in this war enables us to approach the future with a very different view than was possible a decade ago to even the most farsighted physician who was taking advantage of all scientific knowledge then available, especially that contributed by Landsteiner on blood grouping, in arranging for safe blood transfusion from donor to patient.

In the past, repeated blood transfusions had, of course, often been administered but not to the extent that our British colleagues practised, using blood and serum banks, during the first years of this war. Their experience from such multiple transfusions indicated on the one hand the value, in certain conditions, of injecting large amounts of plasma proteins, and on the other the need for red cells when such large amounts of serum proteins were administered.

The program of the American Red Cross has demonstrated the extent to which carefully controlled centralized collection and processing centers can contribute both to the safety of the donor and to that of the recipient of one or another of the products prepared from the blood contributed. The record that has been achieved is a fine one and redounds to the credit of the American Red Cross and the laboratories of the pharmaceutical industry that have loyally collaborated in this nationwide undertaking.

The need for multiple transfusions makes it necessary to use the blood contributed by a number of donors in treating a single individual. Indeed, whether we are dealing with the colloidal properties of the plasma proteins in shock or with the immune properties of the γ-globulins—which contribute but little to the osmotic efficiency of the plasma—the therapeutic value of massive doses, under certain conditions, has become apparent.

The control of infectious diseases by passive immunization with γ-globulins may well be the largest need of a civilian population for a blood derivative and one to which a civilian population can be expected to contribute in the interests of the modification and control of a children's disease, such as measles, until such time as the immunity of each growing generation is achieved.

In the fractionation of blood to obtain the γ-globulins, the red cells and the proteins which they contain, as well as the other plasma proteins, become available for the therapeutic uses for which they are needed; the albumin for the treatment of shock, hypoproteinemia, edema and—prepared in the salt-poor condition—as a diuretic agent; fibrin foam and thrombin as a hemostatic agent; fibrin film as a substitute for a natural body membrane and the large number of other cellular, protein and lipid components, whose physiological function and chemical nature are only beginning to be explored, for whatever therapeutic purposes may prove the most important.

Starting with the assumption, which must for the present remain an assumption, that every part of human blood performs an important natural function, we must continue, as we have begun, to make available as many as possible of its diverse cellular, protein and lipid components, separated and concentrated as specific therapeutic agents, of value in different conditions, in the interests of the most effective and economical use by a society of the blood which it contributes.

OBITUARY

DEATHS AND MEMORIALS

BROWDER JULIAN THOMPSON, associate research director of the laboratories of the Radio Corporation of America at Princeton, N. J., since December, 1943, a consultant in the office of the Secretary of War, was killed on July 4 during a flight in an Army plane in the Mediterranean area. He was forty years old.

WILLIAM SHIELDS MYERS, from 1901 to 1926 director of the Chilean Nitrate Commission for the United States, previously associate professor of chemistry at Rutgers University, died on January 10 at the age of seventy-eight years.

DR. REID T. STEWART, professor emeritus of engineering of the University of Pittsburgh, died on January 12 at the age of eighty-four years.

DR. D. MACCALLUM BLAIR, regius professor of anatomy in the University of Glasgow, died on November 10 at the age of forty-eight years.

THE establishment of the Samuel Slater Memorial Research Laboratory as a part of the Textile Division of the Massachusetts Institute of Technology has been announced. The laboratory houses the latest developments in electronic equipment for research on the physical properties of textiles. It is sponsored by S. Slater and Sons, Inc., and will be under the direction of Professor Edward R. Schwarz and the staff of the textile division of the department of mechanical engineering. It is a tribute to the pioneering work of Samuel Slater, for whom the laboratory is named. H. Nelson Slater, his grandson, now serving as a Commander in the United States Navy, made the presentation.

THE College of Dentistry of New York University held its Horace Wells Centenary Celebration on December 8. The speakers were Drs. E. A. Rovenstine, Isaac Neuwirth and Anthony Mecca.

THE *Journal* of the American Medical Association reports that the Louis Pasteur monument, standing on a pedestal west of the Chicago Museum of Natural History, was presented on December 12 by the Chicago Park District to the Medical Center Commission. It will be placed eventually in Convalescent Park in front of Cook County Hospital. The commission on December 28 voted an appropriation of $25,000 to move the statue, which weighs fifty-four tons and rests on a five hundred and forty-five ton marble and concrete base. In 1927 the statue was given to the park district by a citizens committee headed by the late Dr. Frank Billings. The monument will be rededicated as a symbol of medicine to mark the gateway to a tract of three hundred and five acres which the commission is seeking to acquire for the development of a medical center.

THE centenary of Sir Patrick Manson, "father of tropical medicine" (1884–1922), was marked by a special meeting on December 15 at the Royal Society of Tropical Medicine and Hygiene, London. Sir Philip Manson-Bahr, his son-in-law, gave an illustrated address entitled "The Manson Saga."

SCIENTIFIC EVENTS

VITAL STATISTICS OF AUSTRALIA

THE correspondent from Canberra, Australia, of *The Times*, London, reports that the National Health Medical Research Council, discussing the decline in the birthrate from 32.4 births per 1,000 in the five-year period 1891–95 to 20.7 in 1943, urges the provision of homes with labor-saving devices, domestic help for mothers, the promulgation of measures for contributing to economic security and the establishment without delay of greatly improved hospital, medical and nursing services for maternity.

The council emphasizes that merely to replace the population without striving for an increase requires four children in each family, and an income providing for less is manifestly no solution of the problem. No single man should be regarded as nationally equal to a man with a family, and a family of four or more children should be adequately compensated.

Statements collected from 1,700 women showed that two important factors contributing to the great growth of birth-control were the decreasing dependence of women and an increasing sense of insecurity, economic, psychological, social and international. The number of women admitting deliberately induced abortion was very disturbing. Without immigration, and with fertility continuing in its recent trend, Australia's population would rapidly dwindle after 1950. Public policy should aim at mitigating economic and social disadvantages suffered by the children of parents of the larger families.

An examination of the birth-rate made by a Commonwealth statistician shows that before 1890 it would have doubled the population in 30 years without the aid of migration and that it was increasing the population by from 80 to 90 per cent. in a generation. By 1911 it had fallen to a 40 per cent. increase in a generation, and a decade later to 30 per cent.; by 1932 the level was below that required to replace the existing population. Since then it had risen substantially, but this was owing to

transient factors, including the war-time marriage boom. By 1943 the rate had just attained the replacement level, but the available data indicate that the population will dwindle rapidly after 1950 and that by 1980 deaths will exceed births. In about 20 years the population will reach 8,000,000 and will then begin to decline, returning to its present level by about the end of the century.

MEETINGS OF ENTOMOLOGISTS

APPROXIMATELY three hundred and fifty entomologists registered at the Hotel New Yorker, New York City, for the fifty-sixth annual meeting of the American Association of Economic Entomologists and the thirty-ninth annual meeting of the Entomological Society of America, meeting jointly on December 13, 14 and 15. This registration was augmented by approximately a hundred Army, Navy and Public Health Service individuals who were anxious to get the latest information on DDT.

Almost an entire afternoon was devoted to the presentation of papers on the usefulness of DDT as an agricultural insecticide and this was supplemented by a round-table discussion for an entire day of all the aspects of DDT as an insecticide. The entire morning was devoted to postwar planning. The individual societies devoted several afternoons to the presentation of formal papers and to the business of the respective organizations. The meeting was rated as one of the best ever held by the entomologists, many of whom came from the Pacific coast, Southwest and South.

The Economic Entomologists elected D. L. Van Dine, Washington, D. C., *President;* T. H. Frison, Urbana, Ill., *Vice-president;* and Ernest N. Cory, College Park, Md., *Secretary-Treasurer.* The Entomological Society elected J. A. G. Rehn, Philadelphia, *President;* and Herbert H. Ross, *Secretary-Treasurer.*

ERNEST N. CORY,
Secretary-Treasurer

THE ANNUAL MEETING OF THE AMERICAN PHYTOPATHOLOGICAL SOCIETY

THE thirty-sixth annual meeting and war conference of the American Phytopathological Society was held at the Netherland Plaza, Cincinnati, Ohio, from December 9 to 11, 1944. Approximately three hundred members attended. Sixty-three individuals were elected to membership in the society bringing the total membership to 1,089 as of December 11.

The three-day program included the presentation of eighty papers on original research, which were presented in sections entitled: Fungicides, Virus and Bacterial Diseases, Disease Resistance, Seed and Soil Treatments, Factors Affecting Disease Development and Fungus Diseases.

In addition to the presentation of research papers several conferences were held, including the conference concerning activities of the War Committee. The activities and accomplishments of this committee as developed through sub-committees and regional committees, and through cooperation with other agencies are so extensive that they have had some influence on most of the food, oil and fiber production of the United States and Allied Nations.

A conference on "New Developments in Fungicides" was of special interest to many including representatives of fungicide manufacturers.

At a conference on plant disease surveys it was definitely shown that the work of the Emergency Plant Disease Prevention Program has proved of great value to war-time American agriculture by increasing the effectiveness of plant disease control programs throughout the country. It was reported that a number of new and potentially destructive diseases have been discovered in the United States. These have been called to the attention of research and quarantine agencies so that they may be studied and watched as a necessary precaution against future losses.

Following presentation of papers dealing with "disease resistance" an informal discussion was held on "breeding for plant disease resistance." A conference on the phloem necrosis disease of elm discussed the possibilities of checking the spread of this disease and of informing those interested of the present research program. Current problems and recent developments in seed treatment research work were taken up in a panel discussion.

The officers of the society for 1945 include: Dr. H. B. Humphrey, Box 14, Cosmos Club, Washington, D. C., *President;* Dr. J. H. Craigie, Central Experiment Farm, Ottawa, Canada, *Vice-president;* Dr. E. M. Johnson, Agricultural Experiment Station, Lexington, Ky., *Secretary;* and Dr. R. M. Caldwell, Department of Botany, Purdue University, Lafayette, Ind., *Treasurer.*

THE NATIONAL MALARIA SOCIETY

THE National Malaria Society held its twenty-seventh annual meeting conjointly with the Southern Medical Association in St. Louis, Mo., from November 14 to 16.

The program was presented in three half-day scientific sessions. That of the fourteenth was held jointly with the Sanitary Engineers and Sanitation Officers Section, Southern Branch of the American Public Health Association, comprising eleven papers. On the fifteenth a joint session was held with the American Society of Tropical Medicine at which eleven papers were presented. At the session on the sixteenth, twelve papers were presented.

A business meeting was held subsequent to the scien-

tific session on this date at which the following officers were elected for the ensuing year:

Honorary President, J. A. Le Prince, Memphis, Tenn.
President, H. A. Johnson, Memphis, Tenn.
President-elect, Dr. Mark F. Boyd, Tallahassee, Fla.
Vice-president, Dr. Clay G. Huff, Chicago, Ill.
Secretary-Treasurer, Dr. Mark F. Boyd, Tallahassee, Fla.

THE BERNAYS RADIO AWARD

THE Institute for Education by Radio of the Ohio State University announces that the Edward L. Bernays Radio Award of one thousand dollars will be conferred on the individual responsible for the radio program or series doing most to further democracy in America in the year ending on March 1. The award will be presented at the annual dinner of the institute in Columbus, Ohio, on May 6.

Of the programs nominated and described briefly by the radio editors, those of most promise will be selected for further consideration. Producers of these programs will be asked to supply (1) information about purposes and planning procedures; (2) information concerning the extent to which audience and community become involved in the total project with which the radio program is connected; (3) a recording of a typical program in the series; and (4) the name of the person primarily responsible for the inauguration of the program or program series.

The radio editors of American newspapers are being asked to assist in this enterprise by making the nominations of the programs to be considered for the award. This will ensure that local and regional programs as well as nationwide broadcasts are included. The stations, networks and organizations will keep the radio editors informed of worthy programs so that the editors may listen to the programs and observe the extent of participation by the audience.

SCIENTIFIC NOTES AND NEWS

THE Legion of Merit was conferred on January 11 by President Roosevelt on Rear Admiral Richard Byrd, the polar explorer, in recognition of "exceptionally meritorious conduct" and "outstanding services" on a naval aviation mission in the Pacific.

DR. GANO DUNN, president of the J. G. White Engineering Corporation and president of Cooper Union, and Dr. Frank B. Jewett, chairman of the National Defense Research Committee, who recently retired as vice-president of the American Telephone and Telegraph Company, were elected, in recognition of their "outstanding contributions to the advancement of science, engineering and industry in this country and for their outstanding work in behalf of the New York Electrical Society," honorary members of the society at a ceremony held on January 10 at a dinner meeting at the Engineers Club.

BRIGADIER GENERAL LEON A. FOX, U.S.A., has been awarded the Typhus Commission Medal for "exceptionally meritorious service rendered first as director and later as field director of the United States of America Typhus Commission." He directed the Typhus Control Project of Naples in December, 1943, which within a month brought the epidemic of that disease in southern Italy under control.

THE 1945 Gold Medal of the Technical Association of the Pulp and Paper Industry has been awarded to Bourdon W. Scribner, chief of the Paper Section, National Bureau of Standards, Washington, D. C. The medal is given in recognition of "an outstanding contribution to the technical advancement of the pulp and paper industry." The presentation will be made on February 22 at the annual meeting of the association.

DR. ARTHUR BEVAN, State Geologist of Virginia, was named "Man of the Year in Science" in Virginia for 1944, in an Associated Press poll of the editors of the state. The citation reads: "The honor was voted to Dr. Arthur Bevan who, although engaged in certain phases of war work, has done outstanding work in educating Virginians on the mineral resources of the Commonwealth."

PROFESSOR SIR D'ARCY THOMPSON celebrated on December 2 the sixtieth anniversary of his appointment in 1884 to the chair of natural history at University College, now part of the University of St. Andrews.

THE officers of the American Society of Zoologists elected for the year 1945 are: *President,* Dr. A. S. Pearse, Duke University; *Vice-president,* Dr. J. W. Gowen, Iowa State College; *Treasurer,* Dr. A. C. Kinsey, Indiana University; *Secretary,* Dr. L. V. Domm, the University of Chicago (continuing); *Member of the Executive Committee,* Dr. Sewall Wright, the University of Chicago.

THE Botanical Society of Washington, D. C., announces the election of the following officers for 1945: *President,* Dr. A. G. Johnson, U. S. Bureau of Plant Industry, Soils and Agricultural Engineering, Beltsville, Md.; *Vice-president,* Dr. F. V. Rand, U. S. Office of Experiment Stations, Washington, D. C.; *Recording Secretary,* Dr. N. W. Stuart, U. S. Bureau at Belts-

ville; *Corresponding Secretary,* Janice S. Brown, Plant Industry Sub-Branch Library, Beltsville; *Treasurer,* R. W. Davidson, U. S. Bureau of Plant Industry, Soils and Agricultural Engineering, Beltsville; *Counselors,* Dr. S. W. Emsweller, also of the bureau, and Dr. R. L. Weintraub, Smithsonian Institution, Washington, D. C.

FOLLOWING the annual dinner on January 4 of the District of Columbia Chapter of the Society of the Sigma Xi, officers for 1945 and 1946 were elected as follows: *President,* L. H. Adams, director of the Geophysical Laboratory, Carnegie Institution of Washington; *Vice-president,* John E. Graf, associate director of the U. S. National Museum; *Secretary,* Nathan R. Smith, senior bacteriologist of the U. S. Plant Industry Station, Beltsville, Md., and *Treasurer,* Francis A. Smith, chemist of the National Bureau of Standards. Dr. Paul A. Neal, chief of the Research Laboratory of Industrial Hygiene of the National Institute of Health, and Dr. F. H. H. Roberts, Jr., assistant chief of the Bureau of American Ethnology, were inducted as members.

DR. L. EVERARD NAPIER, formerly director of the School of Tropical Medicine, Calcutta, India, has been appointed for a period of two months under a grant from the Commonwealth Fund a visiting professor at the New York University College of Medicine.

PROFESSOR CHARLES H. WARREN, dean of the Sheffield Scientific School of Yale University, will retire at the close of the current academic year, after serving for twenty-two years. He will be succeeded by Dr. Edmund W. Sinnott, Sterling professor of botany at Yale University and director of the Osborn Botanical Laboratories. Dr. Raymond M. Fuoss, who since 1936 has been associated with the research laboratories at Schenectady of the General Electric Company, has been appointed Sterling professor of chemistry.

DR. FREDERICK E. TERMAN has been appointed dean of the School of Engineering of Stanford University. Dr. Terman has been on leave since 1942 to serve as head of the Radio Research Laboratory of the Government at Cambridge, Mass., and will assume his new work upon release from his present position. He succeeds Samuel B. Morris, who resigned recently to become general manager of the Los Angeles Municipal Department of Water and Power. Dr. Hugh H. Skilling, professor of electrical engineering, who has served as acting head of the department since 1941, has been appointed executive head of the department of electrical engineering to succeed Dr. Terman.

DR. BJARNE PEARSON, associate professor of pathology at the School of Medicine of Tulane University of Louisiana, has been appointed professor of pathology at the College of Medicine of the University of Vermont. Nicholas B. Dreyer, professor of physiology and pharmacology at the Long Island College of Medicine, Brooklyn, has been appointed professor of pharmacology.

PROFESSOR J. M. MACKINTOSH has been made dean of the London School of Hygiene and Tropical Medicine. Brigadier George Macdonald, assistant director since 1939 of the Ross Institute of Tropical Hygiene, has been appointed director of the institute and will take up his appointment on release from the services.

DR. DANIEL FOWLER CAPPELL, professor of pathology at the University of St. Andrews, has been appointed to the chair of pathology at the University of Glasgow, in succession to the late Professor Shaw Dunn.

AT the University of London, Dr. R. W. Firth has been appointed professor of anthropology at the School of Economics, and Dr. Frank Goldby, professor of anatomy at the University of Adelaide, has been made professor of anatomy at the St. Mary's Hospital Medical School.

DR. ALEXANDER WETMORE, since 1925 assistant secretary of the Smithsonian Institution, has been elected secretary to succeed Dr. Charles G. Abbot, who resigned last June. Dr. Abbot has been associated with the institution since 1895. He was elected secretary in 1928.

CLINTON R. HANNA, manager of the electro-mechanical department of the Westinghouse Electric and Manufacturing Company, has been appointed director of the research laboratories.

DR. HENRY F. VAUGHAN, dean of the School of Public Health of the University of Michigan, will serve as president of the newly established National Sanitation Foundation, a non-profit organization supported by industry for research in the field of sanitation. The foundation has been chartered by the State of Michigan and will have its headquarters in the School of Public Health of the university. Dr. Nathan Sinai, professor of public health, has been made vice-president, and Walter Snyder, chief of the Bureau of Sanitation of Toledo, Ohio, has been appointed executive director.

DR. O. R. MCCOY, director of the Tropical Disease Control Division, Preventive Medicine Service, Office of the Surgeon General, has been promoted from the rank of Major to that of Lieutenant Colonel.

DR. EARL T. ENGLE, professor of anatomy at Columbia University College of Physicians and Surgeons, delivered on December 19 the annual Robert J. Terry Lecture before the St. Louis Medical Society.

DR. OTTO SZASZ, research lecturer at the University

of Cincinnati, formerly professor at the University of Frankfurt a.M., delivered a series of lectures early in December at Brown University, the University of Pennsylvania and the Ohio State University on various phases of his recent researches on the extension of certain properties of the Fourier series to more general developments, particularly in reference to the questions of closure and completeness.

DR. JACQUES ROUSSEAU, the newly appointed director of the Montreal Botanical Garden, was in Haiti for the month of November as a government guest. He delivered a series of lectures on human genetics at the School of Medicine in Port-au-Prince and another series on economic botany at the School of Agriculture of Damien.

DR. GEORGE W. CORNER, Dr. Frank B. Jewett, Dr. Harlow Shapley, Dr. W. M. Stanley and Dr. Warren Weaver, *chairman,* constitute an Advisory Committee which is planning a series of broadcasts on science to be given during the intermission of the New York Philharmonic-Symphony Concert on Sunday afternoons. Dr. Douglas S. Freeman is also a member of the committee representing the lay public. It is hoped to bring before the microphone, on successive Sundays, a representative group of this country's leading scientists. Because of the great size and character of the audience for the Philharmonic-Symphony program, this is believed by the committee to be an unusually significant opportunity to enlarge the public's interest in and appreciation of science.

THE Institute of Radio Engineers, at its winter technical meeting, which was held in New York, from January 24 to 27, inaugurated a campaign for the raising of $500,000 for a building fund, in anticipation of postwar expansion of its service to the electronic and communication industries. The directors of the society announced that they are leaving their plans flexible enough to permit their establishing new quarters jointly with other engineering and scientific societies if to do so ultimately proves desirable. The appeal for funds will extend to the membership of the institute and interested corporations.

THE Philadelphia Branch of the American Association of Scientific Workers will hold on January 26 a public meeting and discussion on "American Science and the Good Neighbor Policy" at the Christian Association of Philadelphia. The speakers will be Morris L. Cooke, consulting engineer, author of "Brazil on the March," chief of the American Technical Mission to Brazil, and Gustavo Ortiz Hernan, consul of Mexico in Philadelphia.

Nature writes that "An appeal, signed by Sir William Beveridge, Professor P. M. S. Blackett, E. Carter, J. G. Crowther, Dr. C. D. Darlington and Sir Richard Gregory, has been issued for literature dealing with advances made in Allied countries during the war for dispatch to liberated Europe. In particular, French men of science need this material as quickly as possible. In Paris, there is gas and electricity for only one or two hours in the evenings, so that experimental work is scarcely possible. All materials sent to France would be fully used. Literature would go to the Centre National de Recherche Scientifique in Paris, which is in touch with the whole body of French scientific workers. Single copies would be microfilmed, and films and abstracts distributed. Thus the greatest possible use could be made immediately of any periodicals that can be sent to them. Sets of journals and single copies should be sent to the Association of Scientific Workers, Hanover House, 73 High Holborn, London, W.C. 1."

SINCE January 1 Dr. Christian A. Ruckmick has been assigned to the Operating Department of the Chicago and Northwestern Railway Company reporting directly to the vice-president of operations as supervisor of training. The scope of the training program covers the entire railroad and his services as psychologist are available to all departments of the company.

DR. JESUINO DE ALBUQUERQUE, secretary of public health of the Federal District of Rio de Janeiro, Brazil, is visiting the United States in order to collect data for the establishment of a municipal penicillin laboratory in Rio de Janeiro. In cooperation with the staff of Wyeth Incorporated, Philadelphia, arrangements have been made for a group of Brazilian chemists and bacteriologists to study the production and standardization of penicillin. Facilities at the Philadelphia, West Chester and Kimberton laboratories have been made available for this purpose.

The Times, London, writes that "a number of distinguished American scientists are serving as scientific advisers to the armament section of the United States Strategic Air Forces in Europe. They are credited with valuable contributions to the success of rockets and accurate strategic bombing. Among them are Dr. John L. Synge, the Ohio State University; Dr. Howard M. Jenkins, Swarthmore College; Dr. Oswald Veblen, Princeton University; Dr. H. H. Germond, University of Florida, and Dr. D. L. Webster, Stanford University. Dr. Carl Anderson, professor of physics at the California Institute of Technology, was flown recently from the United States on a special mission to solve problems dealing with rockets."

MRS. AGNES CHASE, since her retirement in May, 1939, as senior botanist in the Bureau of Plant Industry, U. S. Department of Agriculture, has continued as honorary curator of grasses in the Division

of Plants of the U. S. National Museum. A correspondent writes: "She retired with the expectation of working intensively on the grasses of Brazil, but has scarcely done anything on this major enterprise because the continuing demands of the herbarium and the constant calls for help and advice on agrostological problems, many related to the war, require all her time. Her life-time association with this rich collection, a part of the U. S. National Herbarium, has developed an affection which prevents her neglecting the opportunities it presents of serving the cause of science. No one has yet been appointed to carry on even the minimum of routine work in this the world's finest grass herbarium."

THE National Live Stock and Meat Board of Chicago have made a gift of $7,200 to the School of Medicine at Galveston of the University of Texas for the support of work in fat metabolism under the direction of Dr. Arild E. Hansen, professor of pediatrics and director of the child-health program of the William Buchanan Foundation of Texarkana.

DISCUSSION

THE NOMENCLATURE OF THE Rh BLOOD TYPES

IN a recent issue of SCIENCE[1] Wiener suggested a modification of the nomenclature for the Rh blood types. The original Rh is now to be designated as Rh_0, the original Rh_1 is to be called Rh_0', and the original Rh_2 as Rh_0''. The corresponding anti-sera are to be called anti Rh_0, anti Rh′ and anti Rh″. This is a great improvement over the original ambiguous designations of the various Rh blood types and the alleles forming them, but it still leaves one thing to be desired from the genetic viewpoint.

It is customary in naming genes to use subscripts for genes having similar effects but belonging to different pairs, but to use superscripts for different alleles of the same set. Therefore the use of Rh′ and Rh″ is consistent with modern genetic terminology, but the use of Rh_0 is not. The inconsistency could be avoided by using Rh^0 instead of Rh_0. The various Rh alleles would then be Rh^0, Rh′, Rh″, $Rh^{0\prime}$, $Rh^{0\prime\prime}$ and rh. The types would be as given in Table 1:

TABLE 1

Type	Reaction with antiserum		
	anti-Rh^0	anti-Rh′	anti-Rh″
Rh–	–	–	–
Rh′	–	+	–
Rh″	–	–	+
Rh′Rh″	–	+	+
Rh^0	+	–	–
$Rh^{0\prime}$	+	+	–
$Rh^{0\prime\prime}$	+	–	+
$Rh^{0\prime}Rh^{0\prime\prime}$	+	+	+

In a recent article[2] Race *et al.* have used the simple designations R and r in preference to Rh and rh. This seems to be a desirable simplification in line with the older antigens, A, B, M, N and P, and should be adopted. If it were adopted, the "h" would be dropped from all designations in the table above.

LAURENCE H. SNYDER
DEPARTMENT OF ZOOLOGY AND ENTOMOLOGY,
THE OHIO STATE UNIVERSITY

[1] A. S. Wiener, SCIENCE, 99: 532–533, 1944.

THE THREAT TO PURE SCIENCE

I CAN not but feel that Eugene V. D. Robin is wrong in his assertions published in your issue of December 8 regarding the motives which underlie the pursuit of pure science. The pure scientist, as I see it, is indeed seeking "intellectual . . . satisfaction," but by no means merely "*personal* satisfaction"—rather, the satisfaction of the irrepressible intellectual curiosity of *mankind*. It is because all truly rational beings are interested in knowledge for its own sake, as well as in its practical applications, that pure science survives and advances.

Furthermore, the analogy of the chess game is certainly beside the point. Chess *is* played for the merely "personal satisfaction" of the players, but science is pursued to increase man's knowledge of the universe. That is why any threat against freedom of investigation is so much a matter of concern to scientists, as well as to mere philosophers like the undersigned.

JARED S. MOORE
WESTERN RESERVE UNIVERSITY

GAPS IN CURRENT FILES OF SCIENTIFIC PERIODICALS

FROM the standpoint of research the destruction of libraries, periodicals and books constitutes a serious handicap. That losses in these categories are appalling we already know. Also many volumes of important foreign journals usually complete in this country have missing issues due to losses in transit, while replacement may not be possible because foreign publishers have had to contend with such a serious paper shortage it is certain many issues are already out of print.

A Joint Committee on Importations, set up by various library associations, attempted to import a limited number of periodicals during 1942, but it was not found feasible to continue this plan. The Alien Prop-

[2] R. R. Race, G. L. Taylor, E. W. Ikin and A. M. Prior, *Annals of Eugenics*, 12: 206–210, 1944.

erty Custodian is reproducing certain much needed foreign periodicals, but nevertheless gaps have appeared in our files, nor have the problems which libraries face in the post-war period been solved.

In an effort to locate issues of foreign periodicals published during the war, a Check List of Certain Periodicals was organized in connection with the National Union Catalog in the Library of Congress; it will soon be available and will show not only the location of these journals in the United States but will also indicate those issues not available in this country and for which a search will have to be undertaken abroad. This list will form an excellent foundation on which to work, but the problem is complex and many important details will have to be worked out before the task of filling in gaps could be begun. American scholars and librarians will be looked to for leadership in helping to solve these dilemmas. This is a grave responsibility which has to a certain extent been thrust upon us because our library services and publishing processes have been less disrupted than in other countries.

Library development is progressing more rapidly than ever before in Latin America, the Near East, China, in other parts of the Orient and in rural sections of the United States. Students everywhere are eager for access to books and periodicals, but this increased need occurs at a time when publishers and libraries are handicapped as never before. What can be done to meet this situation?

A realistic viewpoint from the outset is desirable. Destruction is widespread, and the terrific financial strain of rehabilitating libraries and educational institutions will be great; therefore it is obvious that it will be impossible to reproduce all the material destroyed. The pooling of the resources left within each country would seem indicated so that a few research libraries could be built up rapidly from the resources remaining in order that scholars and scientists may know where to turn for research materials and back files of periodicals. The usage of scientific journals decreases numerically with each year which passes after publication, therefore, interlibrary loans and the use of microfilm for this type of non-current material remain the great hope for smaller libraries. The use of film has its limitations, however, and the situation is far from ideal.

Any constructive plan should assume, as a foregone conclusion, that the situation calls for reciprocal relationships between countries in the matter of scholarly material. Already there are in this, and other countries, numerous agencies which are concerned with the problem of helping stricken libraries, for example, the American Library Association's Committee on Aid to Libraries in War Areas, the Joint Committee on Books for Devastated Libraries formed on the recommendation of the Council of National Library Associations and the Inter-Allied Book Center, in London. Before plans for reproducing material in quantity are formulated a proposal should be made through the International Federation of Library Associations or through some other agency, that international copyrights be waived by mutual agreement in the case of current out-of-print material which can not be furnished by dealers or from publisher's stocks in amounts sufficient to replace lost or destroyed copies. This would constitute an appropriate recognition and appreciation of generosity of the various groups mentioned above and would result in a benefit to all by helping to keep the costs of reproduction low.

One of the most important problems will be the mobilization and coordination of effort during the early post-war period. This might be accomplished by the rapid organization of national library committees or councils to be set up as soon as military conditions permit. The Division of Cultural Cooperation of our State Department could, through its representatives in various countries, be of great assistance by encouraging the formation of such committees. Some of the capacities in which they could function would be:

(1) By organizing facilities for obtaining information regarding the status of scholarly periodicals published within the country.
(2) By making every effort to salvage material which has escaped destruction and prevent its falling into the hands of persons or groups who would attempt to profit unduly by the emergency situation.
(3) By outlining plans for the preparation of Union Lists of Serials or the revision of those already published.
(4) By planning the extension of national and international loan systems and filming centers.
(5) By furnishing information to national and private agencies established to aid devastated libraries as to how outside aid can be most effectively rendered, and what materials are most urgently needed.
(6) To aid in the establishment of a central committee with international representation which would study the best and cheapest methods of photographic reproduction and determine where this could be most effectively carried out.

If chaotic conditions in the collections of periodicals throughout the world are to be prevented it will require all the ingenuity and intelligence at our command and careful national and international planning will be absolutely necessary in order to mobilize efficiently the resources which remain available. It would be most unfortunate if situations were to arise again comparable to the high cost of German scientific periodicals following the last war. The publication of

scholarly periodical literature should be recognized as one of the most important phases of our post-war planning in order to assure the rapid resumption of the publication of important journals, the elimination of non-essential journals, the cooperation of publishers and editors in keeping prices as low as possible and the avoidance of a duplication of effort and expense, particularly in regard to abstracting and indexing services and in the question of the reproduction of lost material.

In view of the widespread loss of periodicals and books and an increased demand for them, it is essential for every one to save all scholarly periodicals and books for the duration of the war. *No material of this type should be discarded.* Turn it over to the local libraries with the request that it be offered to: the American Library Association's Committee on Aid to Libraries in War Areas, the Medical Library Association's Exchange for Periodicals or the Association of Research Libraries Duplicate Exchange Union. This material may eventually be badly needed in some other part of the world; it should be kept until it is possible to determine what and where this need will be.

EILEEN R. CUNNINGHAM, *Chairman*
Sub-Committee on the Cost of Books and Periodicals, International Federation of Library Associations
VANDERBILT UNIVERSITY
SCHOOL OF MEDICINE LIBRARY

EDUCATION IN ARGENTINA

IN the November 24 issue of SCIENCE under the title, "Education in Argentina," a "Panamerican" calls attention to two remarks of mine[1] which he considers wrongly stated.

Regarding the date of the Argentine military coup d'état which overthrew the régime of President Ramón S. Castillo, I technically stand corrected. June 4 is, of course, the date on which a provisional administration was officially decreed. My selection of June 3 as the date of the revolution came about as the result of knowing too much rather than too little concerning the Argentine situation. Actually, the President and several cabinet ministers fled the country and the troops started to march from Campo de Mayo to the Federal Capital before midnight, June 3.

Unfortunately, "Panamerican" had no means of estimating the time element when he accused me of making too sweeping a statement regarding the administrational changes in Argentine universities. My statements were written in March based on firsthand knowledge of the situation as of February, 1944. The editors of SCIENCE waited for the U. S. Department of State to approve my remarks before publication, hence, there was a delay of approximately four months. Very likely it required two months for the July 7 issue of SCIENCE to reach Buenos Aires. Had "Panamerican" had an opportunity to pass judgment on my statement last March, I am sure he would have had no objections. In any event, it is gratifying to learn that the Universidad Nacional de La Plata has a permanent administration.

Incidentally, it was very difficult following the revolution to obtain accurate information on what was happening in the Argentine universities. The controlled press and radio checked off nearly all news releases pertaining to the universities. Accurate information could only be obtained through personal contacts with professors and students. In fact, the lack of freedom of communications and its influence on education was one of the evils I was attempting to emphasize when my first letter was submitted to the editors of SCIENCE.

J. A. SHELLENBERGER
KANSAS STATE COLLEGE

SCIENTIFIC BOOKS

ADVANCED CALCULUS

Methods of Advanced Calculus. By PHILIP FRANKLIN. McGraw-Hill, 1944. xii + 486 pp. Illustrated. 1944. $4.50.

THIS book is directed mainly toward the engineering student and toward the mathematics student primarily interested in the physical application of his subject. The author has had long experience with both types of students at the Massachusetts Institute of Technology, and is consequently in an excellent position to know their needs, their likes and dislikes and their abilities. For such students he has made an ideal selection of material and has used an excellent method of presentation. He has not assumed that his readers have attained complete mastery of elementary calculus or of other preliminary material. Every teacher knows that such an assumption invites serious disillusionment, at least in so far as concerns the vast majority of his class. Professor Franklin has made his book to fit actual educational circumstances. For example, when determinants are first used in the text, a brief review of the rules of operating on them is given. Thus the book may serve the student for a review of earlier work as well as for an introduction into the methods of applied mathematics.

An outstanding feature of this work is its rapid approach to the deeper aspects of the subject. The

[1] SCIENCE, 100: 11, 1944.

use of any practical tool is not delayed for logical reasons nor because of difficulty in proof. If the conclusions of a theorem are comprehensible to a student without proof or if the proof would seem to him superfluous or unnecessary then the demonstration of the result is omitted. Thus the reader may gain manipulative power even before he has reached a stage where he can appreciate all the reasoning behind the developments. A man may drive a motor car skilfully without being able to repair the motor or he may be a first-rate radio mechanic without understanding Maxwell's theory of electric waves. A good notion of the author's point of view may be had from the following quotation from his preface:

> The attempt to prove everything often leads to the use of roundabout methods in the beginning of a book. This fixes inefficient techniques in the reader's mind, even when better methods are presented later. In this book the author has given the simplest known method of solving each type of problem the first time it appears, even when this means quoting a theorem from an advanced branch of mathematics without proof.

Some idea of the material covered may be had from the following list of chapter headings: I. Elementary Functions for Complex Values and Taylor's Series; II. Partial Differentiation and Implicit Functions; III. Vectors, Curves, and Surfaces in Space; IV. Integration. The Definite Integral Multiple Integrals; V. Line Integrals. Complex Variables; VI. The Gamma Function and Related Definite Integrals; VII. Elliptic Integrals; VIII. Vector Analysis; IX. Differential Equations; X. Legendre Polynomials and Bessel Functions; XI. Fourier Series and Partial Differential Equations; XII. The Calculus of Variations and LaGrange's Equations.

Let us call attention to certain special features of the book. It is arranged in such a way as to be especially useful for self-study. The introduction of review material has already been referred to. There is a great wealth of fine exercises and problems, averaging about one hundred per chapter. Answers to all these are given at the back of the book. Where the solution of a problem departs materially from the methods of the text hints for a successful attack are given. At the end of each chapter is a section offering suggestions for further study. In case proofs have been omitted in the text reference to a suitable source for them is given. In many cases the omissions may be supplied from the author's own text, "Treatise on Advanced Calculus," John Wiley and Sons, 1940. Attention should also be called to a new method of reduction of elliptic integrals of first and second kinds to the tabulated functions. As would be expected in such a book there are very many applications from the physical sciences for any theory introduced. For example, in the chapter on Fourier series only the first two sections are devoted to the statement, without proof, of Fourier's expansion theorem and to the explanation of the method of finding the Fourier coefficients. There follow seven physical applications taken from the theories of the flow of heat, of the vibrating string and of the flow of electricity. An extensive bibliography is given at the end of the book. It is composed largely of titles of books and treatises which the student may read if he wishes to pursue a given subject further.

In the opinion of the present reviewer the value of this book would have been enhanced if more theorems had been stated. While the author is careful to make accurate statements, his results are not usually collected in theorem form. Such a collection of results would have made the book more suitable for reference. Another useful purpose of the theorem is that it brings into sharper relief the distinction between those results which have been proved and those whose demonstrations have been omitted or merely outlined. In his introduction the author himself stresses the importance both for teacher and student of distinguishing between proof and heuristic discussion. Here would have been an additional way of accentuating the difference. No text can include enough subjects to satisfy the whims of every instructor. Yet the reviewer feels that there has been one serious omission in the book under review—the Stiltjes integral. True, this subject has seldom been included in an advanced calculus. But this integral has recently become such a practical tool for the analyst that it is becoming of universal use. Unfortunately it is not yet widely known to physicists and to engineers. It could be of particular effectiveness in applied mathematics.

In conclusion it might be well to summarize what seems to be the chief usefulness of the book. First it is an outstanding text for courses in applied mathematics for engineering students and for science students. It should also prove very serviceable to the practicing engineer who wishes to refresh or improve his mathematical knowledge. The book may also be used for courses given by mathematics departments, especially for "service" courses designed to provide non-mathematics concentrators with mathematical tools. For the pure mathematician, the book would have less value as a text, precisely because it does not emphasize the logical development of the subject.

D. V. WIDDER
HARVARD UNIVERSITY

THE NEEDS OF MAN

Enough and to Spare. By KIRTLEY F. MATHER. Pp. 186, New York: Harper and Brothers, 1944. $2.00.

THE aim of this little book is to show that it is not

the niggardliness of nature but the stupidity of man which imposes the sufferings of poverty and war upon such a large proportion of mankind. Perhaps Dr. Mather would object to such a statement of his aim and would prefer to say that he is trying to show that man's economic suffering is not inevitable but is due to his failure to make use of his scientific knowledge to increase production, to improve the distribution of what he can produce and to control his population growth.

In order to establish his thesis Dr. Mather examines the adequacy (a) of land and minerals for man's probable future needs, and (b) argues that his future needs should not be calculated on the assumption of an indefinite increase in numbers, but rather on the assumption that even the "backward" peoples will shortly come to control their population growth as Western Europeans are now doing.

As regards the first of these points Dr. Mather seems to imply that if he can show an adequacy of resources in the world for the population of the world as a whole there is no need to worry about population pressures disturbing the peace and welfare of mankind. True, he urges a reorganization of world economy and in his later chapters argues eloquently and convincingly for adequate international organization to relieve the needs of growing population in the unindustrialized areas of the earth, but he does not seem to the reviewer to appreciate the fact that these unindustrialized peoples will grow even more rapidly for several decades after they begin to industrialize than they have in the past and that there is as yet no evidence of any intent on the part of the powers possessing unused land and resources to allow these "backward" peoples to share them. It is out of the differential growth of peoples and the differences in their resources that those pressures and frustrations arise which can be played upon by demagogues as excuse for conquest. They will continue to be so used as long as they exist and the crushing of Germany, Japan and Italy will not stop their being exploited. There may be even more violent conflicts when India and China reach Japan's stage of development and find their access to unused resources blocked by the "haves." We should realize that it is not *absolute* poverty which leads a people to seek the expansion of their resources by force but *felt* poverty. The fact is that once a people begins to enjoy a little better living conditions the *feeling* of pressure on resources, both agricultural and mineral, may grow rapidly; that as *actual* pressure begins to lessen *felt* pressure quite commonly begins to grow, especially if resources are scanty. Witness Japan and Italy!

But even if Dr. Mather is right in arguing that there is "enough and to spare" it seems to the reviewer that he ignores too blithely the practical difficulties standing in the way of increasing the agricultural product (food supply) in most countries and the slow and painful progress of industry in poverty-stricken lands which also have meager natural resources. He also seems to discount unduly the increased work involved in making use of inferior grades of mineral resources. If Dr. Mather had ever tried to make two bushels of wheat grow where one grew before or to get his cows to give six gallons of milk instead of three he would be less optimistic than he is about increasing the world's food supply; he would not accept so uncritically the statements of chemists and plant breeders that *manifold* increases of agricultural products are readily attainable. Likewise the reviewer doubts he would believe in the possibility of expanding the tilled area of the earth to about three times its present size if he had gone out to observe the use of land in the highways and byways of the earth with as adequate an agricultural background as he has in geology. It seems highly doubtful that India or China will have "enough and to spare" of food for a number of decades. Furthermore, the use of leaner iron ore, of shale for oil, of thinner and deeper seams of coal, of more distant and more fractious sources of water power will require more labor, or with better processes as much labor as those we are now using. It is not helpful to gloss over these practical economic difficulties in getting "enough," to say nothing of the "to spare."

But even so Dr. Mather is probably right in believing that the economic and technical difficulties as such are not insurmountable. But for all his eloquent argument for world organization he does not seem to appreciate how futile technological skills and scientific knowledge are if political and social conditions do not give them a chance to work.

Finally, as a student of population, the reviewer can not accept the view that because Malthusianism is not forever inevitable it is, therefore, of no importance in the affairs of man at given times and places. The fact is that for perhaps two thirds of mankind even now the only factors preventing more rapid growth of numbers are disease and hunger and war, and that for perhaps one half or more this will continue to be the case for several decades, perhaps for a century. Among Oriental peoples only the Japanese have yet shown any decline in the birth rate. Almost one billion people in south and east Asia still grow about as rapidly as their "subsistence" (Malthus) increases. Moreover, among them the control of disease is just beginning and death rates are two to three times as high as in the western World. To these southern and

eastern Asiatics whose growth is still Malthusian in character must be added most of the population of the Near East, of Africa and of a considerable proportion of Central and South America. Merely as an illustration of what is happening it may be noted that the Indians increased by about 83 million in the 20 years following 1921—from 306 million to 389 million.

Dr. Mather seems to think that these "backward" peoples will not long continue to grow as fast as their "subsistence" increases and therefore, will not feel any increased pressure on their food supply or on their economy as a whole. The reviewer can not agree with this view. He believes they are feeling increased pressure already in many places and will feel much more as their conditions begin to improve. He believes that the political and economic life of the world is not organized to take care of an increase of 50 to 75 million in India in each decade between now and the end of the century. Only increased pressure on subsistence which will raise the current high death rate to about the level of the birth rate will prevent this, for there is no one fairly familiar with India's population who believes there will be any significant decline in her birth rate within five to six decades. Furthermore, even after the birth rate begins to decline the death rate will decline even faster for two to three decades thus raising the rate of growth. If the entire population of south and east Asia (excepting Japan) were to increase as rapidly as that of India (1931–1941) it would grow by at least 140 million in 1940–50 (this is more than the entire population of the United States) and would increase even more rapidly thereafter. Is there any reasonable hope that China and India can care for 80 to 85 per cent. of such an increase within their own borders for the next half or three quarters of a century? The reviewer believes the answer must be, no! Then we must ask if there is any hope of political reorganization which will give these countries access to the land and minerals of which Dr. Mather says there are "enough and to spare." The reader will give his own answer.

WARREN S. THOMPSON

SCRIPPS FOUNDATION FOR RESEARCH IN POPULATION PROBLEMS

SPECIAL ARTICLES

INTERACTION BETWEEN CRYSTALLINE PENICILLIN AND HUMAN PLASMA PROTEINS[1]

PLASMA proteins which were formerly conceived to be only inert colloids, having to do with fluid equilibrium, are now known to be able to bind with small molecules of physiological importance. Schonholzer[2] concluded from his electrophoretic experiments that there is a union of azo-dyes of sulfanilamide with serum albumin. Davis[3,4] showed binding of sulfonamides with serum albumin by equilibrating the drugs between a plasma protein solution and a buffer solution. On the other hand, Kimmig and Weselmann[4] showed, by the technique of cataphoresis, that sulfonamides are "adsorbed" to serum albumin and that dissociation can be produced by animal charcoal. The ability of plasma protein to combine with phenol red[5,6,7] has also been demonstrated by the spectrophotometric absorption method.

Since penicillin is now widely used clinically, it is of extreme interest and importance to ascertain whether it will combine with human plasma protein. For that purpose, we have used as test proteins electrophoretically homogeneous γ-globulin and albumin, as well as a mixture of α- and β-globulins, at the concentration present in normal human plasma. Thus 7 ml of a protein solution, pH 7.8, containing 125 micrograms of crystalline sodium salt of penicillin per ml were put into a Cellophane bag and equilibrated with 14 ml of a phosphate buffer solution of penicillin of the same concentration and the same pH. After 18 to 24 hours of continuous rocking at 1° C. the concentrations of penicillin, in plasma and in buffer, were determined. It was found that, if albumin is used, the antibiotic activity of the protein solution after equilibration is greater than that of the dialysate (see table 1). Moreover, the greater part of

TABLE 1

THE ANTIBIOTIC ACTIVITY OF EXTERNAL AND INTERNAL FLUIDS, BEFORE AND AFTER DIALYSIS, IN OXFORD UNITS PER ML*

		External fluid (Penicillin in buffer)	Internal fluid (Penicillin and albumin in buffer)
Experiment I	Before dialysis	187	187
	After dialysis	151	284
Experiment II	Before dialysis	178	187
	After dialysis	150	246

* 1.0 mg of the crystalline sodium salt of penicillin = 1,650 Oxford Units.

[1] From the Laboratory of Physical Chemistry and the Division of Microbiology, The Squibb Institute for Medical Research, New Brunswick, N. J.

[2] G. Schonholzer, *Klin. Wchnschr.*, 19: 790, 1940.

[3] B. D. Davis, SCIENCE, 95: 78, 1942.

[4] B. D. Davis, *Jour. Clin. Investigation*, 22: 753, 1943.

[5] J. Kimmig and H. Weselmann, *Dermat. u. Syph.*, 182: 436, 1941.

[6] A. Grollman, *Jour. Biol. Chem.*, 64: 141, 1925.

[7] H. W. Robinson and C. G. Hogden, *Jour. Biol. Chem.*, 137: 239, 1941.

the original antibiotic activity can be accounted for. Within the limits of testing procedures, there is no demonstrable union between penicillin and any of the globulins.

To demonstrate further that a union between penicillin and albumin took place, we have attempted to isolate the penicillin-albumin complex by precipitating it in aqueous 50 per cent. alcohol solution at 5° C. The unbound penicillin is soluble in such a concentration of alcohol. The precipitated protein-penicillin complex was re-dissolved with water and re-precipitated with 50 per cent. alcohol without appreciable loss of penicillin activity. To obtain a dried powder of the new compound, the alcohol precipitate was dissolved with water and the solution was lyophylized.

Unlike the sulfonamide-albumin complex, which Davis and others believe is devoid of bacteriostatic property, the penicillin-albumin complex does possess antibiotic activity. If chemical union and not physical adsorption takes place between the antibiotic agent and the albumin, the complex is expected to be more slowly excreted than penicillin itself because of the increase of molecular size. A few preliminary biological studies of this protein have been made. It was found that mice receiving the complex intramuscularly did not excrete the antibiotic agent into the urine as rapidly as mice receiving the same dose of free penicillin by a similar route. The importance of discovering a means to retard the rate of excretion of penicillin has been generally recognized. Partially successful attempts to obtain delayed action of penicillin by use of diodrast[8] or para-amino-hippuric acid[9] have been reported. Likewise, the use of a suspension of penicillin in oil or in oil containing 0.75 to 6.0 per cent. beeswax[10] has been reported to give delayed excretion. However, we are not aware of any report in the literature on a chemical compound of penicillin possessing a delayed excretion rate. It must be stated here that at present we have no evidence that a true chemical compound is formed when penicillin and albumin interact. Since the albumin used is of human origin, the resulting complex might be expected to possess little antigenicity in man. Its metabolism, its immunological properties as well as its stability toward acid, alkali and penicillinase will be reported elsewhere after detailed studies have been completed.

SUMMARY

Penicillin combines with human serum albumin, as demonstrated by dialysis experiments. Unlike the sulfonamide-albumin complex, the penicillin-albumin possesses antibiotic activity. Such a complex can be freed of unbound penicillin by repeated precipitation at 50 per cent. alcohol and obtained as a dried powder. Mouse excretion studies indicated that the penicillin-albumin complex was excreted more slowly than the sodium salt of penicillin.

BACON F. CHOW
CLARA M. MCKEE

[8] C. H. Rammelkamp and S. E. Bradley, *Proc. Soc. Exp. Biol. and Med.*, 53: 29, 1943.

[9] K. H. Beyer, R. Woodward, L. Peters, W. F. Verwey and P. A. Mattis, SCIENCE, 100: 107, 1944.

[10] M. J. Romansky and G. E. Rittman, SCIENCE, 100: 196, 1944.

THE SEROLOGICAL DIAGNOSIS OF SYPHILIS[1]

IN an extensive investigation directed toward the development of a serodiagnostic method for the differentiation between syphilitic and biologic false positive sera, observations have been made which indicate that in the two groups of sera[2] the reactive antibodies differ from each other in certain significant respects. Since previous work has shown that even in strongly reactive syphilitic sera the antibodies constitute but a minute fraction of the total proteins,[3] and that isolation by specific flocculation with lipoidal antigen yields extremely low recovery of the purified product,[4, 5] a practical approach to the problem has been based on non-specific methods of characterization and fractionation of the sera, as described below:

(1) *Electrophoresis.* Electrophoretic analyses were made on 13 normal, 25 syphilitic and 45 biologic false positive sera. The sera from patients with syphilis[6] differed markedly from normal sera in exhibiting decreased albumin and increased *gamma* globulin con-

[1] The work described in this paper was done under contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Duke University.

[2] A total of about 300 syphilitic and biologic false positive sera has been used for the investigation of the various phenomena described in this report. Sera accepted as syphilitic were those for which there was unequivocal clinical evidence for infection, whereas the group of allegedly false positive sera may have included some genuinely syphilitic specimens. However, among this group the occurrence of syphilis was fairly well excluded in those cases where the positive serological reaction could be shown to be of transitory nature, and accompanied by such etiologically unrelated diseases as malaria, virus pneumonia, mumps, smallpox vaccination, etc. Serum specimens have been obtained from various Army General Hospitals through Brigadier General Hugh Morgan, M.C., and Major Charles R. Rein, M.C.; from private hospitals through Drs. J. E. Moore and Paul Rosahn; from the Rapid Treatment Center, U. S. Public Health Service, Durham, N. C., through Surgeon Samuel Fisher, and from the clinics of Duke Hospital through Dr. J. L. Callaway.

[3] H. Eagle, "Laboratory Diagnosis of Syphilis," p. 168. St. Louis: C. V. Mosby Company, 1937.

[4] E. Witebsky, *Zent. f. Bakt.*, 122: 70, 1931; *Z. f. Immunf.*, 80: 323, 1933.

[5] O. Bier and E. Trapp, *Jour. Immunol.*, 40: 465, 1941.

[6] These particular sera were obtained from patients who had received therapy of one kind or another.

tents. The difference was in both relative and absolute amounts. Biologic false positive sera from presumably normal individuals showed differences from normal sera which were qualitatively similar to those of syphilitic sera but of considerably smaller magnitude. However, biologic false positive sera from individuals known to have diseases other than syphilis gave findings essentially like those obtained with syphilitic sera. No unique components and no significant mobility differences from normal sera were seen among the serum protein constituents of either the syphilitic or biologic false positive sera.

(2) *Fractionation.* The distribution of the reactive antibodies among the various serum components has been determined by (a) fractional precipitation with increasing concentrations of ammonium sulfate, under standardized conditions; and (b) isoelectric precipitation of the globulins by treatment of the diluted sera with CO_2. The latter method offers the advantage that it does not require dialysis and that it yields a single, strongly reactive fraction containing preponderantly *gamma* globulin (protein concentration 4–8 mg per cc). Analyses made on some 200 syphilitic and biologic false positive sera revealed that (a) fractions GI and GII, precipitable, respectively, by 1.4 and 1.7 M ammonium sulfate, contained most of the serological activity, whereas the crude albumin, remaining after precipitation of GIII by 2.1 M ammonium sulfate, was always serologically inactive; (b) the sum total of the individual titers of the isolated fractions of syphilitic sera, prepared by either of the above methods, was consistently less than that of the whole serum, whereas with biologic false positive sera, elimination of the crude albumin resulted in a significant increase in the titer of the globulins over that of the parent sera. This differential behavior, particularly pronounced with weakly reactive sera, suggested an inhibitory effect of crude albumin on the reaction of antibodies of biologic false positive sera with lipoidal antigen.

(3) *Inhibition and redispersion.* It was found that addition of the crude albumin fraction to globulin fractions derived from false positive sera causes complete inhibition of specific flocculation with lipoidal antigen, as well as redispersion of floccules formed before crude albumin was added. The addition of this fraction had little effect on the reaction of globulins isolated from syphilitic sera. So far the heat-stable inhibiting component of the albumin fraction has been found only in human sera, though individual preparations vary in potency. Crystalline human serum albumin does not exert any inhibitory effect. Further work on the isolation and identification of the inhibitor is in progress.

(4) *Heat stability.* Experiments were made with some 50 syphilitic and biologic false positive sera, or their isolated globulin fractions, by heating the samples for 20 minutes at temperatures ranging from 56 to 66° C. The data indicate that the antibodies of false positive sera are more susceptible to heat inactivation than those of syphilitic sera. The presence of non-specific serum proteins appears to be without effect on the temperature-activity relation.

(5) *Adsorption on calcium phosphate.* A considerable degree of purification of the syphilitic antibody has been achieved by adsorption from whole sera on freshly precipitated calcium phosphate, followed by precipitation of the eluate with ammonium sulfate.[7] This procedure has yielded under optimal conditions a solution containing 0.015 mg of protein nitrogen per cc per 4 flocculation units. While about 80 per cent. of the total antibody activity of syphilitic sera of varying titer is adsorbed by the calcium phosphate, in a limited number of experiments with false positive sera, no activity has been found in the eluate.

The observations described herein indicate that the antibodies of truly syphilitic sera, reactive with lipoidal antigen, differ from those of biologic false positive sera in certain chemical and immunological respects. The possibility of the application of these findings to the development of a practical method of differentiation is being explored.

HANS NEURATH
E. VOLKIN
J. O. ERICKSON
F. W. PUTNAM
DEPARTMENT OF BIOCHEMISTRY

H. W. CRAIG
DEPARTMENT OF BACTERIOLOGY

G. R. COOPER
D. G. SHARP
A. R. TAYLOR
J. W. BEARD
DEPARTMENT OF SURGERY,
DUKE UNIVERSITY SCHOOL OF MEDICINE,
DURHAM, N. C.

A NEW TRYPANOCIDAL AGENT: γ-(p-ARSENOSOPHENYL)-BUTYRIC ACID[1]

γ-(p-ARSENOSOPHENYL)-BUTYRIC acid was first described in a paper from this laboratory in 1940[2] It is a stable white crystalline powder, slightly soluble in water, but readily soluble in dilute alkali. Neutral solutions of the sodium salt can be sterilized by autoclaving, and such sterile solutions in sealed ampules

[7] H. Neurath, F. W. Putnam, E. Volkin and J. O. Erickson, Abstracts of papers presented at the one hundred and eighth meeting, American Chemical Society, New York, N. Y., September, 1944, p. 21B.

[1] Preliminary report.

[2] G. O. Doak, H. G. Steinman and H. Eagle, *Jour. Am. Chem. Soc.*, 62: 3012, 1940.

have been kept at room temperature for 12 months without demonstrable change.

The toxicity and trypanocidal activity of this compound against *T. equiperdum* have been described in a previous communication.[3] In both mice and rabbits, the chemotherapeutic index was significantly higher than that of tryparsamide; and the relatively small curative dose (CD_{50} = 1.6 mg per kg in mice and 3.6 mg per kg in rabbits) suggested that treatment in man might be effected with a considerable economy in time and cost.

Of the species of trypanosomes pathogenic for man, cultures of *Schizotrypanum cruzi* (the cause of Chagas disease), which is relatively resistant to tryparsamide and most other arsenicals, were found to be immobilized and killed *in vitro* within 4 hours by dilutions in excess of 1:400,000.[4] In other laboratories, the compound was found to be effective against *T. rhodesiense*[5] in mice, and Van Hoof, Henrard and Peel[6] obtained encouraging results in the treatment of *T. gambiense* infections in guinea pigs, chimpanzees and man.

Of particular therapeutic significance was the finding that the γ-(p-arsenosophenyl)-butyric acid was fully active against so-called "arsenic-resistant" strains of trypanosomes. (a) A variant of *T. equiperdum*, which was 5 to 200 times more resistant to amino- and amide-substituted arsenicals than the parent strain, was found to be normally susceptible to the butyric acid compound *in vitro*.[7] (b) *Schizotrypanum cruzi* infections in man are known to resist treatment with tryparsamide and other arsenicals; but as noted above,[4] a typically "arsenic-resistant" culture of that organism proved susceptible to the γ-(p-arsenosophenyl)-butyric acid *in vitro*. (c) The curative dose in *T. rhodesiense* infections in mice[5] was identical with the curative dose in experimental *T. gambiense* or *T. equiperdum* infections, despite the fact that the first-named species in man is reported to be more resistant to treatment than *T. gambiense*. (d) In both experimental animals and man, Van Hoof, Henrard and Peel[6] observed that strains of *T. gambiense* resistant to tryparsamide were susceptible to the butyric acid-substituted phenyl arsenoxide.

In the light of these experimental and clinical data, a large-scale field trial was begun in the summer of 1944, with the collaboration of the Sleeping Sickness Services of the Gold Coast (Dr. G. Saunders), Nigeria (Dr. J. L. McLetchie), Belgian Congo (Major General L. Van Hoof) and the British Forces in West Africa (Brigadier G. M. Findlay). Similar studies are projected in Northern Rhodesia (Dr. J. F. C. Haslam), French West Africa (Colonel G. LeRouzic), French Equatorial Africa (Colonel Ceccaldi) and Sierra Leone (Dr. R. D. Harding). The wide geographic distribution of the cases assured the inclusion of a variety of strains, perhaps differing in virulence and in their resistance to treatment.

The schedule of treatment and the total dosage of drug were deliberately varied in the several treatment centers in order to determine the minimum curative dose and the most efficient and practicable method of administration. The drug was supplied as an ampuled sterile 2 per cent. solution. This was injected either twice weekly, three times weekly or daily, to a total of 6 to 24 injections. The individual dose was similarly varied between 0.25 and 0.5 mg per kg, the average individual dose being 0.8 to 1.5 cc of the 2 per cent. solution. The latter dose in a man weighing 60 kg represents 1/50 of the maximal tolerated dose in mice and 1/8 of the maximal tolerated dose in rabbits.[3] The recommended method of administration was intravenous; but the compound has been injected intramuscularly in infants and in patients with small veins, with no untoward reaction except for transitory pain at the site of injection.

To date, more than 200 patients have been treated in collaboration with the workers previously listed, and it is anticipated that the study will ultimately include in excess of 1,000 patients. Of necessity, this must be a preliminary report, since the evaluation of therapeutic efficacy, even in early cases, presupposes observation for at least one year after the conclusion of treatment. Nevertheless, the following tentative conclusions seem justified by the results obtained to date.

(a) Except for occasional nausea and vomiting, observed after approximately 2 per cent. of the injections, there have been no toxic reactions in more than 100 early cases, representing a total of more than 800 injections.

(b) When organisms were present in the lymph nodes or blood, these regularly disappeared within 30 to 60 minutes after the first injection (*cf.* Table 1). This included some patients previously shown to be infected with a strain of trypanosomes resistant to tryparsamide.

(c) There is reason to believe that in *early* cases, without central nervous system involvement, sterilization and definitive cure can be obtained within less than 2 weeks, by daily injections of approximately 0.4 mg per kg each. The first four cases of early

[3] H. Eagle, R. B. Hogan, G. O. Doak and H. G. Steinman, *Public Health Reports*, 59: 765, 1944.
[4] H. Eagle and H. J. Magnuson, unpublished data.
[5] C. M. Scott, personal communication.
[6] L. Van Hoof, C. Henrard and E. Peel, personal communication.
[7] H. Eagle and H. J. Magnuson, *Jour. Pharm. and Exper. Therap.*, in press.

TABLE 1

THE RATE AT WHICH TRYPANOSOMES DISAPPEARED FROM LYMPH NODES AFTER TREATMENT WITH γ-(P-ARSENOSOPHENYL)-BUTYRIC ACID

Time of second node puncture, minutes after treatment	Number patients tested[1]	Result of second lymph node puncture	
		Positive	Negative
30	21	3[2]	18
45	15	1	14
60	2	0	2
Untreated controls, repunctured 60 minutes after the original positive puncture	16	14	2

[1] None of these are duplicates: all nodes were positive just before treatment.
[2] In two of these patients repunctured 60 minutes after treatment, no organisms could be found.

infection treated with this compound by Dr. L. Van Hoof, each of whom received a total of only 3.5 to 4.5 mg per kg, distributed over 6 to 11 injections, have now been observed for periods of 1, 5, 6 and 8 months. They are clinically well, the blood and lymph nodes remain free of organisms, and the spinal fluid remains normal. It is to be noted that one of those four patients was infected with a strain of *T. gambiense* which was unaffected even by large doses (6 gm) of tryparsamide.

(d) In the *late* cases, with clinical and laboratory evidence of central nervous system involvement, the results to date are not encouraging. A few of the patients have improved; the majority have been unaffected. There is some indication also that the drug is more toxic in late cases, in that two of these patients have died with cerebral symptoms suggestive of a toxic encephalopathy. The treatment of advanced cases is continuing, at reduced dosage (0.25 mg per kg); and it is planned to treat some cases with small doses of the γ-(p-arsenosophenyl)-butyric acid in conjunction with a pentavalent arsenical. The therapeutic efficacy of the arsenoxide alone in cases with an altered spinal fluid, but without clinical evidence of central nervous system involvement, remains to be determined.

(e) In collaboration with Brigadier G. M. Findlay, of the British Forces in West Africa, and Dr. J. Simpson, veterinarian of the Accra District, Gold Coast, a few sheep and cattle with clinical evidence of trypanosomiasis, confirmed by blood examination, and one horse with advanced symptoms have been treated. The sheep and the horse improved markedly after 2 to 3 injections at approximately 0.25 mg per kg each, and at the present writing seem well after a total of 6 to 8 injections. Organisms persist in the cattle despite some clinical improvement.

In summary, the results to date suggest that γ-(p-arsenosophenyl)-butyric acid is a highly active trypanocidal agent, with which it may be possible to cure early cases of human trypanosomiasis within two weeks or less, and with reasonable freedom from toxic reactions. This, coupled with the fact that it appears to be active against strains of trypanosomes resistant to tryparsamide and other arsenicals, may greatly simplify the mass treatment of the disease, and permit a considerable economy of time and cost. The results in late cases are not encouraging. There is some indication that the compound may be effective against some, but not all, forms of animal trypanosomiasis.

HARRY EAGLE

VENEREAL DISEASE RESEARCH AND
POSTGRADUATE TRAINING CENTER OF THE
U. S. PUBLIC HEALTH SERVICE AND
JOHNS HOPKINS UNIVERSITY,
BALTIMORE 5, MARYLAND

SCIENTIFIC APPARATUS AND LABORATORY METHODS

A MICROCALOMEL ELECTRODE FOR POLAROGRAPHIC MEASUREMENTS

A SATURATED calomel electrode is generally used as an external electrode in polarographic measurements. Kolthoff and Lingane[1] describe a special H-cell for use in making half-wave potential measurements. They also describe various salt bridges for use in connecting electrolysis cells to permanent external anodes. Hume and Harris[2] have discussed a special salt bridge for use in connecting an external calomel electrode with the solution being studied in the electrolysis cell.

We have designed a microcalomel electrode (Figs. 1 and 2) to be used internally with the dropping mercury electrode. An obvious advantage of using the micro electrode is that it is independent of the electrolysis vessel which can therefore be cleaned and refilled with fresh samples without disturbing the electrode itself. When desired, the calomel electrode and its salt bridge container can be removed and stored in saturated potassium chloride solution.

The electrical resistance of a cell composed of a microcalomel electrode and a hydrogen electrode dipping into a saturated solution of potassium chloride was found by standard methods[3] to be 1,500 ohms. The same resistance was found for the cell irrespec-

[1] I. M. Kolthoff and J. J. Lingane, "Polarography," Interscience Publishers, Inc., New York, N. Y., 1941.
[2] D. N. Hume and W. E. Harris, *Ind. Eng. Chem., Anal. Ed.*, 15: 465, 1943.
[3] S. G. Starling, "Electricity and Magnetism," sixth edition, Longmans, Green and Company, New York, N. Y., 1937.

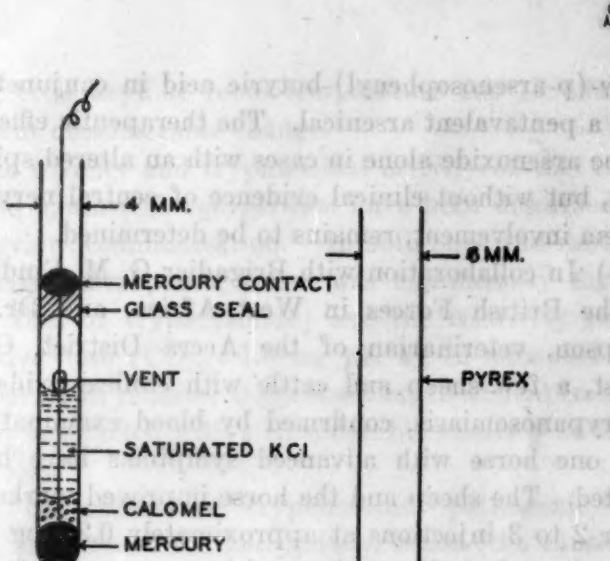

FIG. 1. Details of construction of the microcalomel electrode.

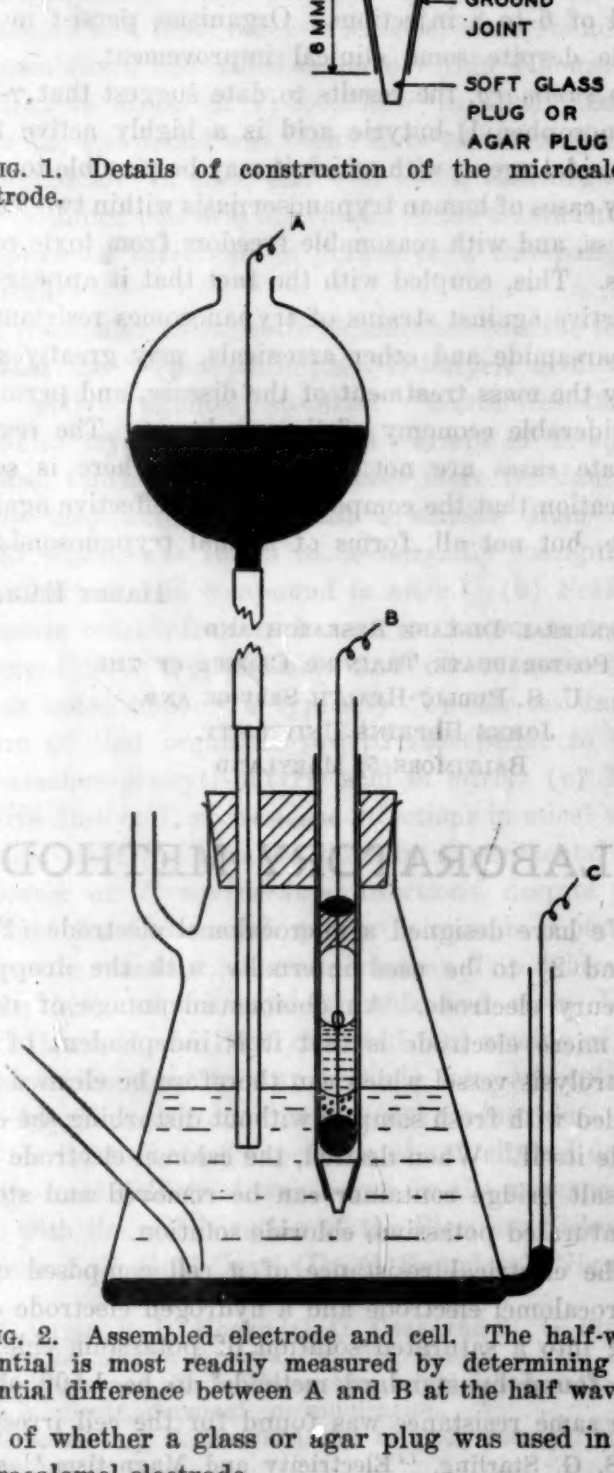

FIG. 2. Assembled electrode and cell. The half-wave potential is most readily measured by determining the potential difference between A and B at the half wave.

tive of whether a glass or agar plug was used in the microcalomel electrode.

Since the value of the internal resistance of the entire cell was only 1,500 ohms, the resistance of the microcalomel electrode and bridge alone must be less than this value. This compares favorably with the reported "several hundred ohm" resistance of the H-cell of Kolthoff and Lingane, and the 600 ohm resistance claimed for the bridge alone in the case of Hume and Harris. It is to be noted that where ground glass plugs are used, the contact surface of the plug should not exceed the length given in Fig. 1, since the resistance of the electrode will increase rapidly with the length of this surface. Where potassium chloride is detrimental to the electrolysis it is recommended that agar plugs made up to contain ions common to the supporting electrolyte be used.

In Table 1 we list half-wave potentials of various ions as measured against our electrode and the corresponding half-wave potentials recorded in various standard references. This table shows that the micro electrode gives values comparable with the values recorded in the literature.

TABLE 1

COMPARISON OF DETERMINED HALF-WAVE POTENTIALS WITH THOSE RECORDED IN LITERATURE

Ion	Supporting electrolyte	Recorded half-wave potential (V.S. Sat. calomel electrode) Kolthoff Lingane	Sargent (Brochure)	Majer (Chart)	Average	Our value
Tl+	0.1N.KCl	−0.460	−0.467	−0.45	−0.459	−0.460
Cd++	0.1N.KCl	−0.599	−0.647	−0.59	−0.612	−0.605
Co++	0.1N.KCl	−1.20	−1.20	−1.22	−1.21	−1.24
Zn++	0.1N.KCl	−0.995	−1.03	−1.03	−1.02	−1.00
Ni++	1.0N.KCl	−1.10	−1.06	−1.05	−1.07	−1.15

Note: The values attributed to Majer were estimated from his chart on the Polarographic "Spectrum" of the elements. The exact conditons of electrolysis are not known in the case of the values given in his chart.

PHILIP W. WEST
EDWARD S. AMIS

COATES CHEMICAL LABORATORY,
LOUISIANA STATE UNIVERSITY

BOOKS RECEIVED

EDDY, WALTER H. and GILBERT DALLDORF. *The Avitaminoses. The Chemical, Clinical and Pathological Aspects of the Vitamin Deficiency Diseases.* Illustrated. Pp. xi + 438. Williams and Wilkins Co. $4.50. 1944.

NORMAN, J. R. SQUIRE. *Memories of Charles Davies Sherborn.* Pp. 202. George G. Harrap and Company, Ltd. 15/ net. 1944.

PUFFER, RUTH R. *Familial Susceptibility to Tuberculosis.* Illustrated. Pp. x + 106. Harvard University Press. $2.00.

RICHARDSON, HENRY B. *Patients Have Families.* Pp. xviii + 408. The Commonwealth Fund. $3.00. 1945.

WALKER, J. FREDERIC. *Formaldehyde.* Illustrated. Pp. xi + 397. Reinhold Publishing Corporation. $5.50. 1944.